

DETAILED ACTION

Claims 1-9, 13-32, species: 1) BCG and interferon gamma, or LPS, TNF-alpha as maturing agent, and 2) CD86 or CD80 co-stimulatory molecule are examined in the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 13 remain rejected under 35 U.S.C. 102(b) as being anticipated by Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07, and as evidenced by Labeur et al, 1999, J Immunol, 162: 168-175, for reasons already of record in paper of 2/11/09.

The response asserts as follows:

Triozzi et al do not use partially mature human dendritic cells, but instead immature human dendritic cells differentiated from monocytes by culture in GM-CSF and IL-4. Sallusto et al, 1994, demonstrate that human monocytes when cultured in the presence of GM-CSF and IL-4 differentiate into immature dendritic cells.

Labeur et al do nothing to support the characterization by the Examiner that the dendritic cells used by Triozzi et al are partially mature dendritic cells. Labeur et al do not conflict with

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Sallusto et al. Different from human DCs, the murine dendritic cells treated with GM-CSF and IL-4 taught by Labeur et al are from mice and are mature DCs.

Specifically the response asserts as follows: It is well known in the art that cytokines necessary to induce differentiation of human immature and/or mature dendritic cells from human monocytic dendritic cell precursors are different from those necessary to induce differentiation of murine immature and/or mature dendritic cells from murine bone marrow dendritic cell precursors. Labeur et al teach that culture of murine, bone marrow dendritic cell precursors in GM-CSF and IL-4 induces the cells to differentiate and mature, as measured by phenotype and substantial reduction in phagocytosis and endocytosis. When comparing the bone marrow dendritic cell precursors in GM-CSF and IL-4 with those precursors cultured in the presence of GM-CSF and IL-4 plus TNF-alpha, LPS or CD40L, they only differ in the stimulus of lymphocyte reactions and efficiency of in vitro peptide presentation, but have the same substantial reduced phagocytotic activity. Further, Labeur et al specifically state that IL-4 is a potent enhancer of mouse DC maturation.

Further, Labeur et al teach that murine, bone marrow DCs induced by culture in GM-CSF and IL-4 do not retain the ability to take up and process antigen. Table II at page 171, and p.171, right hand paragraph, clearly show that BmDCs cultured in GM-CSF and IL-4 have reduced ability to uptake antigen and have essentially the same reduced capacity for phagocytosis as those BmDCs cultured in the presence of GM-CSF and IL-4 plus LPS or CD40L. As such, even if the culture of human monocytic dendritic precursor cells in GM-CSF-IL-4 could be compared with the murine dendritic precursor cells in GM-CSF and IL-4, the teaching of Labeur et al do

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not support the Examiner conclusion that the dendritic cells of Labeur et al or Torizzi et al are partially mature dendritic cells as defined and used in the instant application and claims.

The submission of Sallusto et al is acknowledged.

The response has been considered but is not found to be persuasive for the following reasons:

The instant specification discloses as follows: “In DCs cultured and **partially matured** according to the present invention in the presence of a dendritic cell maturation agent, such as GM-CSF and IL-4, the levels of phosphorylated JAK2 (janus activated kinase 2) can be measured to indicate the initiation of maturation by methods well known in the art” (p.11, second paragraph).

Thus, although Sallusto et al name human DCs cultured in GM-CSF and IL-4 differently, i.e. as immature DCs, however, when based on the above disclosure in the instant specification, it would be reasonable to interpret the human DCs treated with GM-CSF and IL-4 taught by Triozzi et al as partially matured DCs.

Further, it is reasonable to interpret human DCs treated in GM-CSF and IL-4, taught by Triozzi et al as partially mature DCs, and not mature DCs, based on:

1) the teaching of Labeur et al that murine DCs treated in GM-CSF and IL-4 have intermediate degree in maturation, in between the immature murine DCs treated only with GM-CSF and the more mature DCs treated in GM-CSF and iL-4 plus LPS or CD40L (p.173, second column, last paragraph), and especially

3) the ability of those murine DCs treated with GM-CSF and IL-4 to take up and process antigen, in addition to antigen presentation, and T cells stimulation, in view of the teaching of

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Labeur et al (p.168, second column, second paragraph, p.171, second column, second paragraph, figure 2 on page 172, figure 3 on page 172 and figure 4 on page 173). That is, Figure 3 and p.171, second column in Labeur et al show that when **incubated with an antigen**, the OVA peptide, murine DCs treated with GM-CSF and IL-4 are intermediate between immature DCs treated GM-CSF alone and more matured DCs treated with GM-CSF and IL-4 plus LPS or CD40L in the ability to present the antigen. In other words, those murine DCs must inherently have been able to pick up and process the antigen present in the incubation medium, in order to present the antigen. This ability of picking up and processing the antigen necessary for presenting the antigen is lost in fully mature, i.e., terminally differentiated DCs, as defined in the instant specification (p.11, paragraph before last).

In addition, the response does not have any evidence or recite any reference teaching that the murine DCs treated GM-CSF and IL-4 taught by Labeur et al are mature DCs and do not represent a model for human DCs treated with GM-CSF and IL-4. Contrary to the response assertion, murine DCs treated with GM-CSF and IL-4 taught by Labeur et al retain the ability to take up and process antigen. Table II at page 171 of Labeur et al only discloses phagocytotic activity of different treated murine DCs. The ability to take up and process antigen by murine DCs treated with GM-CSF and IL-4 is actually shown in figure 3 and p.171, second column, item under "Allostimulatory activity and presentation of OVA peptide". Figure 3 and p.171, second column show that when **incubated with an antigen**, the OVA peptide, murine DCs treated with GM-CSF and IL-4 is intermediate between immature murine DCs treated GM-CSF alone and more matured murine DCs treated with GM-CSF and IL-4 plus LPS or CD40L in the ability to present the antigen. In other words, those murine DCs must inherently have been able

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to pick up and process the antigen present in the incubation medium, in order to present the antigen. This ability of picking up and processing the antigen necessary for presenting the antigen, however, is lost in fully mature, i.e., terminally differentiated DCs, as defined in the instant specification (p.11, paragraph before last). Thus, based on figure 3 and p.171, second column of Labeur et al, and the disclosure in the specification, it is reasonable to interpret that murine DCs treated with GM-CSF and IL-4, and more matured DCs treated with GM-CSF and IL-4 plus LPS or CD40L taught by Labeur et al are all partially mature, because they still retain the ability to pick up and process antigen.

In view that the DCs treated with GM-CSF and IL4 taught by Triozzi et al and Labeur et al are the same as the claimed partially mature DCs, supra, the method of treating cancer using DCs treated with GM-CSF and IL4 prior their administration into a patient as taught by Triozzi et al is the same as the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 2, 4 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07, **in view of** Labeur et al, 1999, J Immunol, 162: 168-175, and further in view of Murphy et al (US 5,788,963, filed on 07/31/1995), for reasons already of record of paper of 2/11/09.

The response presents the same arguments set forth above concerning the teaching of Triozzi et al and Labeur et al. Briefly, the human DCs treated by GM-CSF and IL-4 taught by Triozzi et al are immature DCs, since Sallusto et al call them immature DCs. The murine DCs treated by GM-CSF and IL-4 taught by Labeur et al are different from human DCs, and are mature DCs since they have reduced phagocytic ability, and lost the ability to pick up and process antigen.

The response further asserts that Murphy et al do nothing to provide the missing elements from Triozzi et al and Labeur et al.

The response has been considered but is not found to be persuasive for the following reasons:

In view that the DCs treated with GM-CSF and IL4 taught by Triozzi et al and Labeur et al are the same as the claimed partially mature DCs, *supra*, the method of treating cancer using DCs treated with GM-CSF and IL4 prior their administration into a patient as taught by Triozzi et al is the same as the claimed method.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to obtain the DCs taught by Triozzi et al and Labeur et al from skin, spleen,

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bone marrow, thymus, lymph nodes, umbilical cord blood, as taught by Murphy et al, to increase the number of available sources for making DCs.

It would have been obvious to replace DCs obtained from the individual to be treated, taught by Triozzi et al and Labeur et al with DCs isolated from a healthy individual HLA-matched to the individual to be treated as taught by Murphy et al, to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy et al. Further, an HLA-matched DCs would be necessary, because antigen presentation of DCs is restricted to the complementing HLA molecule, in view of the teaching of Murphy et al.

2. Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07 in view of Labeur et al, 1999, J Immunol, 162: 168-175, and further in view of US 20050059151 (Bosch et al, which has as priority US 60/317592, filed on 09/06/01), and Chakraborty et al, 2000, Clin Immunol, 94(2): 88-98, IDS # AF of 05/09/07) for reasons already of record in paper of 2/11/09.

The response asserts that Triozzi et al and Labeur et al do not disclose or suggest the claimed method. The response further asserts that Bosch and Chakraborty et al do nothing to provide the missing elements from Triozzi et al and Labeur et al. The response asserts that if the references were combined as suggested by the Examiner, at most, one might use a maturation agent suggested by Bosch et al to mature DCs that have been exposed to antigen prior to administration to a subject.

The response has been considered but is not found to be persuasive for the following reasons:

In view that the DCs treated with GM-CSF and IL4 taught by Triozzi et al and Labeur et al are the same as the claimed partially mature DCs, supra, the method of treating cancer taught by Triozzi et al is the same as the claimed method, wherein the DCs treated with GM-CSF and IL4 are administered into a patient, without prior exposure of the DCs to a tumor antigen. Further although Bosch et al use treated DCs that have been exposed to antigen prior to their administration to a subject, the primary reference, Triozzi et al teach the use of treated DCs for administration into a cancer patient, without the need of their exposure to a cancer antigen, prior to their administration to the patient.

It would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to add to GM-CSF plus IL-4 maturing agent taught by Triozzi et al and Labeur et al with BCG and interferon gamma, as taught by Bosch et al, in the method taught by Triozzi et al and Labeur et al for maturing DCs in vitro for use in producing an anti-cancer response, because of the following reasons:

- 1) A combination of BCG and interferon gamma selectively produces more maturing DCs that secrete IL-12 than those inhibiting DCs secreting IL-10, as taught by Bosch et al,
- 2) DCs that secrete IL-12 efficiently stimulate T cells, whereas DCs that produce IL-10 are inhibitory, as taught by Chakraborty et al.
- 3) The ability of DCs to promote antitumor immunity correlates with their high efficiency of stimulating resting T cells and high production of IL-12, as taught by Labeur et al.

In other words, BCG and interferon gamma as maturing agent as taught by Bosch et al would be advantageous, because they selectively enhance the production of stimulating DCs that secrete IL-12, and therefore efficiently stimulating T cells, in view of the teaching of Chakraborty et al, and promoting anti-tumor immunity, in view of the teaching of Labeur et al.

3. Claims 14-18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07 in view of Labeur et al, 1999, J Immunol, 162: 168-175, for reasons already of record in paper of 2/11/09.

The response asserts that Triozzi et al and Labeur et al do not disclose or suggest the claimed method. The response further asserts that it would not have been obvious to choose direct administration of partially matured DCs over subcutaneous injection.

The response has been considered but is not found to be persuasive for the following reasons:

In view that the DCs treated with GM-CSF and IL4 taught by Triozzi et al and Labeur et al are the same as the claimed partially mature DCs, supra, the method of treating cancer using DCs treated with GM-CSF and IL4 prior their administration into a patient as taught by Triozzi et al is the same as the claimed method.

It would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to administer DCs taught by Triozzi et al and Labeur et al to a tissue area surrounding the tumor, into a lymph node directly draining a tumor area, directly to a circulatory vessel duct that delivers blood or lymph to the tumor or a tumor afflicted organ, or into the circulatory system such that the cells are delivered to the tumor or tumor afflicted organ, to

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increase the number of available sites for DCs injection, from which DCs could be readily delivered to the tumor, in view that DCs migrate very inefficiently into the regional lymph nodes after subcutaneous injection into mice, as taught by Labeur et al.

4. Claims 19-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07 in view of Labeur et al, 1999, J Immunol, 162: 168-175, and further in view of Nikitina et al, 2001, Int J Cancer, 94: 825-833, IDS# AN of 05/09/07, for reasons already of record in paper of 2/11/09.

The response asserts that Triozzi et al and Labeur et al alone or in combination with Nikitina et al do not disclose or suggest the claimed method.

The response has been considered but is not found to be persuasive for the following reasons:

In view that the DCs treated with GM-CSF and IL4 taught by Triozzi et al and Labeur et al are the same as the claimed partially mature DCs, supra, the method of treating cancer using DCs treated with GM-CSF and IL4 prior their administration into a patient as taught by Triozzi et al is the same as the claimed method.

It would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine DCs administration taught by Triozzi et al and Labeur et al with radiation therapy, because gamma irradiation induces the dramatic ability of DCs injected i.v. or s.c. to migrate and penetrate cancer tissue, and to take up apoptotic bodies, resulting in enhanced, potent antitumor response, as taught by Nikitina et al.

5. Claims 21-23, 25, 27-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07, in view of Labeur et al, 1999, J Immunol, 162: 168-175, and Sukhatme et al (US 6,797,488), for reasons already of record in paper of 2/11/09.

The response asserts that the composition of immature human DCs taught by Triozzi et al and Labeur et al is not the same as the claimed partially mature DCs. For example, they are different in levels of expression of a number of surface antigens, CD14, CD11c, CD80 and CD86, the phosphorylation level of a number of intracellular protein, including for example, jak2, and the amounts of IL-10 and /or IL-12. Further, Triozzi et al teach that the immature dendritic cells administered in vivo lost B7-2 (CD86A) and show a decrease in the intensity of CD11c, suggesting that the possibility that immunostimulatory activity of dendritic cells is down regulated. The response asserts that the specification discloses that partially matured DCs down regulate cytokines receptors on the surface as compared to immature dendritic cells, making them less sensitive to any immunosuppressive effects of cytokines in the intratumoral space. Immature dendritic cells as defined in the specification include monocyte dendritic cells cultured in the presence of GM-CSF and IL-4.

The response has been considered but is not found to be persuasive for the following reasons:

Contrary to the response assertion, Triozzi et al do not teach that human DCs treated with GM-CSF and IL-4 are immature DCs. The DCs treated with GM-CSF and IL4 taught by Triozzi et al and Labeur et al are the same as the claimed partially mature DCs, supra. Triozzi et al further teach that DCs generated in vitro by GM-CSF and IL-4 express the co-stimulatory

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molecules **CD80 and CD86**, and a low number of CD83 (p.2649, first column, item under Results). Further, other than the elected CD80 and CD86 cited in claim 22, the limitation of other surface antigens, CD14, CD11c, the phosphorylation level of a number of intracellular protein, including for example, jak2, the amounts of IL-10 and /or IL-12, the down regulation of cytokine receptors on cell surface is not recited in the claims, and therefore the arguments are moot.

Further, the instant specification discloses as follows: “In DCs cultured and **partially matured** according to the present invention in the presence of a dendritic cell maturation agent, such as GM-CSF and IL-4, the levels of phosphorylated JAK2 (janus activated kinase 2) can be measured to indicate the initiation of maturation by methods well known in the art” (p.11, second paragraph).

Thus, when based on the above disclosure in the instant specification, it would be reasonable to interpret the human DCs treated with GM-CSF and IL-4 taught by Triozzi et al as partially matured DCs.

6. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07, in view of Labeur et al, 1999, J Immunol, 162: 168-175, of record, and Murphy et al (US 5,788,963, filed on 07/31/1995), for reasons already of record in paper of 2/11/09.

The response asserts that Triozzi et al and Labeur et al alone or in combination with Murphy et al et al do not disclose or suggest the claimed composition.

The response has been considered but is not found to be persuasive for the following reasons:

The DCs treated with GM-CSF and IL4 taught by Triozzi et al and Labeur et al are the same as the claimed partially mature DCs, supra.

It would have been obvious that to replace DCs obtained from the individual to be treated taught by Triozzi et al and Labeur et al with DCs that have been isolated from from a healthy individual HLA-matched to the individual to be treated, as taught by Murphy et al, to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy et al. Further, an HLA-matched DCs would be necessary, because antigen presentation of DCs is restricted to the complementing HLA molecule, in view of the teaching of Murphy et al.

New Rejection Due to the Amendment

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 13-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9, 13-32 are indefinite, because claim 1 is confusing.

Claim 1 can be interpreted either as:

1) the partially matured dendritic cells have been induced to mature in vitro, and have become **matured** dendritic cells in vitro, or

2) the dendritic cells have been induced to a maturation process and have become partially matured in vitro before being administered to an individual, wherein said partially matured dendritic cells are capable of taking up and processing antigen in vivo, i.e. after being administered to an individual.

For the purpose of compact prosecution, claim 1 is interpreted as follows:

A method for producing an anti-tumor immune response comprising administration to an individual with a cancerous tumor a cell population comprising partially matured dendritic cells that have been induced to partially mature in vitro, wherein the partially matured dendritic cells take up and process antigen in vivo and are enabled to induce an anti-tumor immune response subsequent to administration to the individual.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

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will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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October 20, 2009

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